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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,459	11/07/2001	David L. Lewis	Mirus.030.04	3774

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/007,459	LEWIS ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14-16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 14-16, and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed March 19, 2009.

Claims 11, 14, and 18 have been amended.

Claims 11, 14-16, and 18 are pending in the instant application.

Claims 11, 14-16, and 18 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed December 22, 2008, claims 14 and 18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment filed March 19, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to claims 14 and 18 to have them depend from a pending claim and not a canceled claim.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed December 22, 2008, claims 11, 15, and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24,

2005) in view of Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006). **This rejection is withdrawn** in view of Applicant's arguments filed March 19, 2009 (see pages 3 and 4). It is noted that the Examiner agrees that Applicant's 1.131 Declaration filed August 25, 2008 showed that the injection volume taught by Zimmer et al. would not increase hydrostatic pressure against a wall of the vessel thereby increasing permeability of the vessel. However, upon further consideration, a new ground(s) of rejection is made in view of Zhang et al. (Human Gene Therapy, 1997 Vol. 8:1763-1772) who provide motivation to increase hydrostatic pressure against a wall of the vessel thereby increasing permeability of the vessel. This new rejection is made of record as presented below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 14-16, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmer, A. (Methods, 1999 Vol. 18:286-295, made of record in the previous Office Action mailed August 24, 2005) in view of Zhang et al. (Human Gene Therapy, 1997 Vol. 8:1763-1772), and Vaish et al. (Nucleic Acids Research, 1998 Vol. 26:5237-5242, made of record in the previous Office Action mailed July 25, 2006).

Claim 11 is drawn to a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone; injecting a volume of a solution containing the complex into an efferent or afferent mammalian vessel of the target tissue *in vivo*, wherein the rate of injection and the volume of the solution increase permeability of a vessel within the target tissue thereby delivering the double strand RNA oligonucleotide from inside the vessel, through a wall of the vessel, into the extravascular space and into the *in vivo* parenchymal cell, wherein the double strand oligonucleotide inhibits expression of the

gene. Claims 14-16 and 18 depend from claim 11 and include all the limitations of claim 11 with the further limitations wherein the parencymal cell is a liver cell; wherein the complex has a positive charge or a negative charge; and wherein the fluid is inserted within 2 minutes.

Determining the scope and contents of the prior art

Zimmer teach delivering an antisense oligonucleotide complexed with positive and negative charged polymers into a liver cell via tail vein injection (see Abstract and discussion at page 292). Specifically, Zimmer teach mixing an antisense and a polymer, wherein the zeta potential of the complex is less negative than the zeta potential of the antisense alone (see Table 2 and page 290, first full paragraph, which states, "at a lower ratio the surface charge of the nanoparticles is decreased by the ODNs as indicated by a decreased ζ potential"). Zimmer teach Protocol A, which provides cationically (positively) charged oligonucleotide-loaded nanoparticles and Protocol B, which provides anionically (negatively) oligonucleotide-loaded nanoparticles (see page 287, first and second paragraphs). Zimmer teach that the antisense nanoparticle complexes were injected into the tail vein at 5 nmol/5 ml/kg.

It is noted that Zimmer are silent regarding whether or not the antisense oligonucleotide complexed with positive and negative charged polymers delivered into liver cells via tail vein injection inhibited expression of a target gene. However, the burden of establishing whether the prior art antisense oligonucleotide complexed with positive and negative charged polymers has the function of inhibiting gene expression, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where

the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Also, see *In re King*, 801 F.2d 1324, 1327, 231 USPQ 136, 139 (Fed. Cir. 1986). Therefore, it falls to Applicant to determine and provide evidence that the antisense oligonucleotide complexed with positive and negative charged polymers taught by Zimmer would or would not have the additional functional limitation of inhibiting expression of a gene, as instantly claimed.

Ascertaining the differences between the prior art and the claims at issue

Applicant's 1.131 Declaration filed August 25, 2008 showed that the injection volume taught by Zimmer et al. would not increase hydrostatic pressure against a wall of the vessel thereby increasing permeability of the vessel. Therefore, Zimmer et al. do not teach this limitation. Zimmer et al. also do not teach a double stranded RNA

oligonucleotide or delivery within 2 minutes.

Zhang et al. teach expression of naked plasmid DNA injected into the afferent and efferent vessels of rodent and dog livers. Specifically, Zhang et al. teach that plasmid DNA are manually injected over ~30 sec via intraportal injection and hepatic vein injection and DNA reaches the liver (see Figure 1 and page 1765, first column, for example). Zhang et al. also teach that an injection rate of 66ml/min in the dog bile duct resulted in luciferase expression in the liver (see Table 1, dog #6). Zhang et al. also teach:

> "The natural direction of blood flow provides a sufficient impetus to retard the egress of injection fluid and raise the hydrostatic pressure" See page 1768, second column, Discussion.

Additionally, Zhang et al. teach that a raise in hydrostatic pressure increases the delivery of plasmid DNA to the hepatocyte surface not only for blood vessel administrations, but for bile duct injections too (see last paragraph bridging pages 1769 and 1770). Zhang et al. speculate that the increased hydrostatic pressure could transiently attenuate bile secretion thereby decreasing the clearance of the plasmid DNA or by disrupting the tight junctions between hepatocytes thereby increasing the flow of plasmid DNA between the canalicular and basal-lateral spaces (see page 1770, first column).

Vaish et al. teach that single stranded antisense oligonucleotides and double stranded ribozymes are two approaches that use similar techniques to achieve the same goal (see page 5239, first column). For example Vaish et al. teach, "The first step for inhibition of gene expression by a ribozyme is its binding to the mRNA. This step is

akin to the antisense oligodeoxynucleotide method (AS-ODN) used for the same purpose. It is, therefore, not surprising that both approaches benefit from experience in each others areas".

Resolving the level of ordinary skill in the pertinent art

The level of ordinary skill in the pertinent art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

Considering objective evidence present in the application indicating obviousness or nonobviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to devise a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone using the teachings of Zimmer and following the teachings and motivation of Vaish et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to inject the volume of solution such that the hydrostatic pressure against a wall of the vessel is increased using the teachings of Zhang et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to administer the volume of solution within 2 minutes using the teachings of Zhang et al.

One of ordinary skill in the art would have been motivated to devise a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative

than the zeta potential of the double strand RNA alone since Zimmer taught that such a process could be used for nucleic acid gene therapy. One of ordinary skill in the art would have been motivated to substitute the antisense oligonucleotide taught by Zimmer with a double stranded RNA oligonucleotide as instantly claimed since Vaish et al. taught that antisense oligonucleotides and double stranded ribozymes function in a manner similar and it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One of ordinary skill in the art would have been motivated to inject the volume of solution such that the hydrostatic pressure against a wall of the vessel is increased because Zhang et al. taught that hydrostatic pressure is raised by the natural direction of blood flow in a mammal. Further, one of ordinary skill in the art would have been motivated to inject the volume of solution such that the hydrostatic pressure against a wall of the vessel is increased because Zhang et al. taught that such a mode of injection increases the delivery of high levels of foreign DNA to hepatocytes. One of ordinary skill in the art would have been motivated to inject the volume of solution within 2 minutes because Zhang et al. taught that injection over 30 seconds results in the best levels of foreign gene expression in the liver.

One would have had a reasonable expectation of success at devising a process for inhibiting the expression of a gene in an *in vivo* parenchymal cell in a target tissue in a mammal comprising, mixing a double stranded RNA and an amphipathic compound or a polymer to form a complex wherein the zeta potential of the complex is less negative than the zeta potential of the double strand RNA alone because Zimmer

clearly teach the successful use and delivery of an antisense nucleic acid to a liver cell *in vivo* and since antisense and dsRNA are both sequence specific nucleic acid inhibitors of gene expression and are art-recognized functional and structural equivalents, the simple substitution of one known element for another would have yielded predictable results at the time of the invention. See recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ2d 1385).

One would have had a reasonable expectation of success at injecting the volume of solution such that the hydrostatic pressure against a wall of the vessel is increased since Zhang et al. taught the successful use and design of such a mode of injection to deliver foreign DNA to hepatocyte surfaces of mammalian livers. One would have had a reasonable expectation of success at injecting the volume of solution within 2 minutes since Zhang et al. taught the successful use and design of such a mode of injection for foreign DNA uptake and expression in liver cells.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James "Doug" Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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June 2, 2009
/Terra Cotta Gibbs/